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Functionalization of Sydnones with Donor-Acceptor Cyclopropanes, Cyclobutanes, and Michael Acceptors

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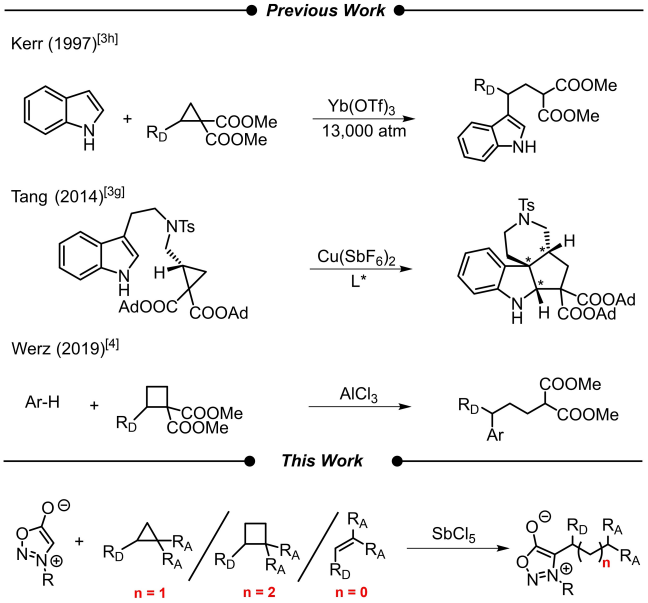
We present a Lewis acid catalyzed nucleophilic ring-opening of donor-acceptor cyclopropanes and -butanes by sydnones, utilizing their respective 1,3- and 1,4-reactivity. The same conditions can be applied for the addition of sydnones to Michael acceptors. We propose a Friedel-Crafts like mechanism. The reaction provides a rare, low-temperature, transition metal-free, and functional group tolerant protocol for the late-stage functionalization of these mesoionic compounds of emerging importance in catalysis and bio-orthogonal chemistry.

Donor-acceptor cyclopropanes (DACs), whose dominant yet all but exclusive reactivity is that of an all-carbon 1,3-dipole, have found widespread use in research.[1][2] The Friedel-Crafts like arylation of the donor-carbon is well studied, especially with electron-rich, nitrogen-bearing alkaloid cores such as indoles (Scheme 1).[3] We published a work on the analogous ring-opening of donor-acceptor cyclobutanes.[4] Sydnones, the most prominent class of mesoionic compounds, have been under scientific investigation for almost a century.[5] The moiety is found in numerous pharmaceuticals (e.g. *molsidomine*, *mesocarb*, *feprosidnine*, *linsidomine*) with unique attributes.[6] They have recently gathered attention for their properties as precursors to (abnormal) NHCs[7] and ligands for essential Pd-catalyzed reactions (Sonogashira-Hagihara, Suzuki-Miyaura, Buchwald-Hartwig).[8] Their molecular orbital properties have attracted the interest of theoretical and experimental chemists alike. Even after thorough computational investigation, their aromaticity is still a matter of debate.[7b,9] Sydnones are most commonly known for their 1,3-dipolar reactivity and cycloaddition reactions.[10] The possibility to react these masked azomethine imines under physiological, bio-orthogonal conditions, opened up the use of sydnones as linkers in labeling and imaging within living cells. CuSAC (Cu-catalyzed sydnone-alkyne cycloaddition) and SPSAC (strain-promoted sydnone-alkyne cycloaddition) present a viable alternative or addition to the click chemistry of azides.[11] Sydnones, carrying two instead of one potential sites for substituents, allow for more diverse products than their azide counterparts. Yet, the number of procedures for late-stage functionalization on C4 is limited.[12] Metalation of C4 can be employed for a range of typical Grignard or lithium aryl/alkyl reactions (with or without previous halogenation).[13] Suzuki- and Heck-type reactions are also commonly used for modification.[14] Even fewer procedures exploit the reactivity of sydnones as carbon nucleophiles.[15] In an attempt to broaden the spectrum of late-stage modification of sydnones, we were able to optimize conditions under which DACs undergo nucleophilic ring-opening (Table 1). Under the same conditions, we were able to transform donor-acceptor cyclobutanes (DACBs) and strong Michael acceptors in an analogous fashion.



Scheme 1. Friedel-Crafts type reactions of strained donor-acceptor cyclopropanes and -butanes.

In order to achieve the desired reaction, we screened a vast number of Lewis acids. Only $SbCl_5$ yielded a noteworthy amount of product at room temperature and below. Traces of product were detected with other strong Lewis acids

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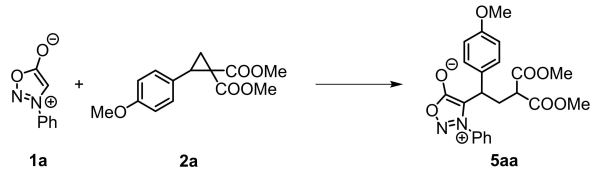
Table 1. Optimization and Screening.



1a 2a 5aa

Entry	Catalyst	Solvent	T., t	Volume	Yield[d]
1	TiF_4	DCE	RT, 24 h	4 + 1 mL[a]	trace
2	$Sc(OTf)_3$	DCE	RT, 24 h	4 + 1 mL[a]	trace
3	TMSOTf	DCE	RT, 24 h	4 + 1 mL[a]	trace
4	BF_3Et_2O	DCE	RT, 24 h	4 + 1 mL[a]	trace
5	$SbCl_5$	DCE	RT, 24 h	4 + 1 mL[a]	50%
6	$SbCl_5$	PhCl	RT, 24 h	4 + 1 mL[b]	58%
7	$SbCl_5$	MeCN	RT, 24 h	4 + 1 mL[c]	64%
8	$SbCl_5$	$MeNO_2$	RT, 24 h	4 + 1 mL[c]	66%
9	$SbCl_5$	$MeNO_2$	0 °C, 2 h	4 + 1 mL[a]	76%
10	$SbCl_5$	$MeNO_2$	0 °C, 2 h	2.5 + 1 mL[a]	86%
11	$SbCl_5$	$MeNO_2$	0 °C, 2 h	2.5 + 1 mL[c]	91%

[a] A solution of sydnone (0.1 mmol) and DAC (0.2 mmol) was added in one portion (1 mL solvent) to a solution/dispersion of Lewis acid (0.04 mmol), stirred as indicated, solvent removed. [b], [c]: A solution of DAC (0.2 mmol in 1 mL solvent) was added at [b]: 12 mmol/h or [c] 0.2 mmol/h to a solution/dispersion of Lewis acid (0.04 mmol) and sydnone (0.1 mmol), stirred as indicated, solvent removed. [d] Determined by ^{1}H-NMR (1,3,5-trimethoxybenzene standard).

(entries 1–4). Almost identical yields were obtained in chlorobenzene, acetonitrile, and nitromethane (entries 6–8). For the reaction of donor-acceptor cyclobutanes nitromethane and chlorobenzene cannot be employed due to side reactions, DCE had to be used instead.

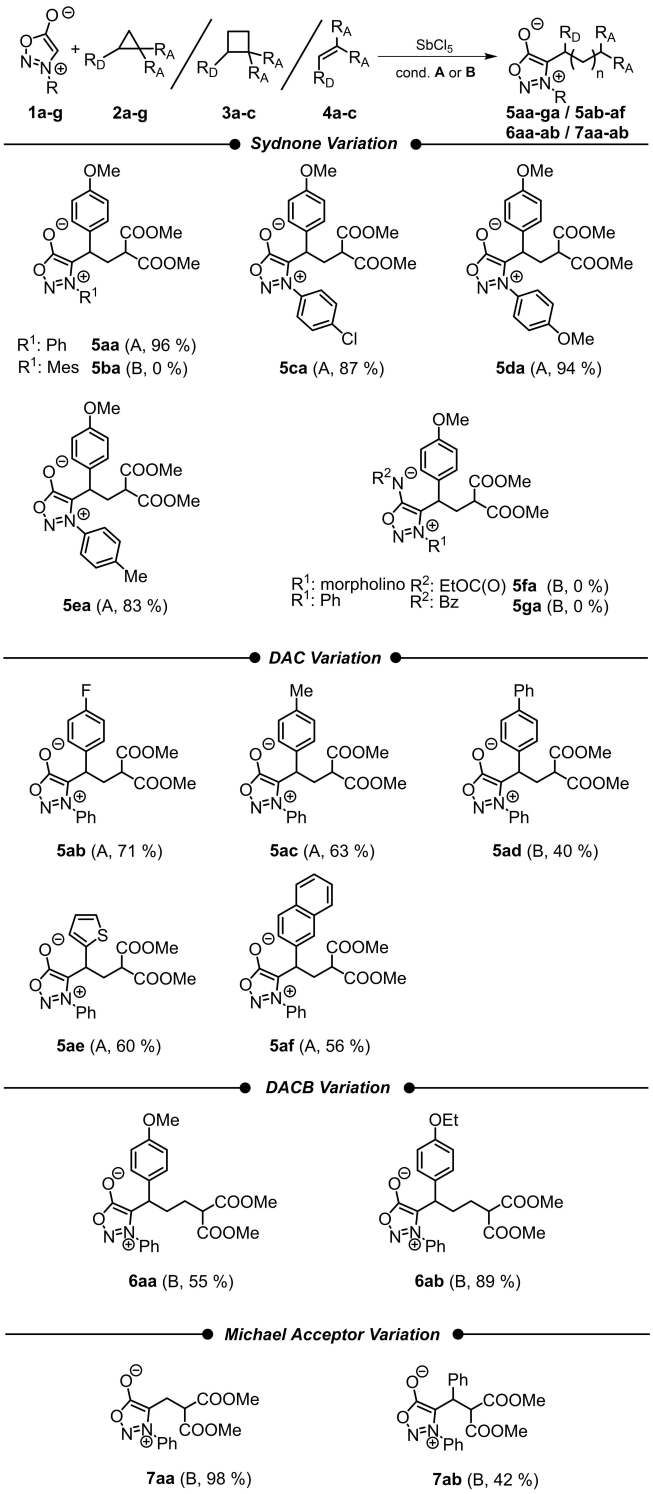
Yields improve with increasing amounts of the electrophile, but we decided to cap our optimization at two equivalents of cyclopropane to maintain a reasonable atom efficiency. After evaluating different concentrations and the speed of addition we arrived at the optimized conditions (entry 11).

We began to explore the scope of the reaction starting with different sydnones and sydnone imines (Scheme 2). Generally, electron-rich (σ^+) sydnones react faster and provide higher yields.

All compounds present in the mixture after the reaction that bear a sydnone moiety (left-over sydnone, the respective product, side-products) behave surprisingly similar in normal phase chromatography, they possess an almost identical retention factor and cannot be separated by means of flash column chromatography alone. HPLC is necessary to obtain analytically pure samples. Given the sheer number of manual steps required by the work-up and the associated potential losses of product, we refrain from interpreting narrow differences in the yields (e.g., between compounds **5ca** and **5da**).

Highly sterically shielded sydnones (e.g., *N*-mesityl-sydnone **1b** (→**5ba**)) and the less nucleophilic sydnone imines (e.g., molsidomine **1f** (→**5fa**), benzoyl-*N*-phenyl-sydnone imine **1g** (→**5ga**)) could not be converted.

DACs bearing strongly electron-donating groups (**5ab**, **5ac**, **5ae**, **5af**) were almost fully converted upon addition at 0 °C, these were optimally added dropwise over a prolonged amount of time to avoid side reactions. Less active three-membered



Scheme 2. Scope of Friedel-Crafts type coupling of sydnones with DACs, DACBs, and Michael acceptors. Conditions A: A solution of DAC (0.2 mmol in 1 mL $MeNO_2$) was added at 0.2 mmol/h to a solution (2.5 mL $MeNO_2$) of $SbCl_5$ (0.04 mmol) and sydnone (0.1 mmol) at 0 °C, the mixture was stirred until completion, the solvent was removed and the residue purified by flash column chromatography and HPLC. Conditions B: $SbCl_5$ was added to a mixture of sydnone (0.1 mmol) and DAC (0.2 mmol) in $MeNO_2$ (3.5 mL) at RT, stirred until completion. Workup identical to A. DCE has to be used for DACBs and Michael acceptors. See Supporting Information for details.

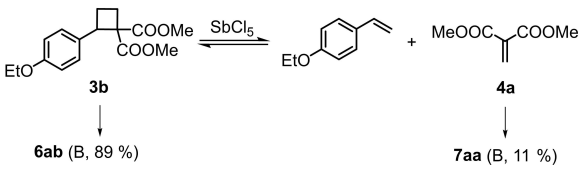
rings (**5 ad**), cyclobutanes (**6 aa**, **6 ab**), and Michael acceptors (**7 aa**, **7 ab**) required room temperature and a longer reaction time (18 h); in these cases, no dropwise addition was required. DACs and DACBs with less-electron-donating groups on their donor motif (e.g., 4-nitrophenyl, 4-trifluormethylphenyl) could not be transformed.

The malonate acceptor cannot be replaced by a single ester or a nitrile/malononitrile moiety: acrylates, crotonates, and the corresponding nitriles did not undergo conversion. Only Michael acceptors with low steric bulk are suitable, a geminal substitution at the electrophilic carbon was not tolerated (e.g., isopropylidene dimethyl malonate).

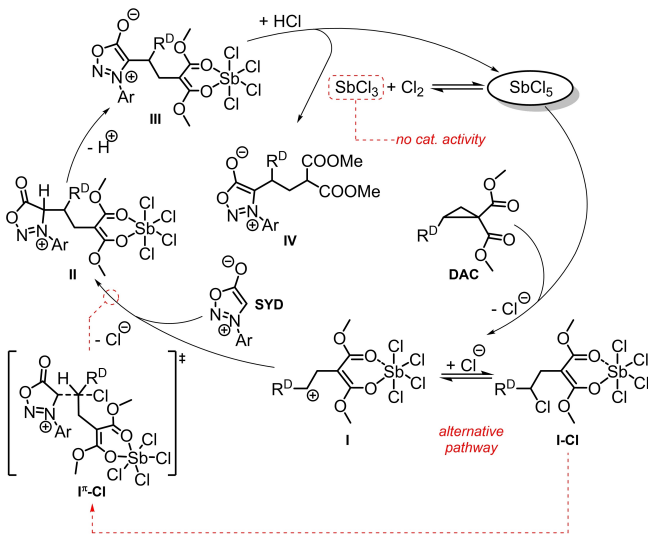
A *para*-substituent on the electrophilic component is necessary. Once a successful addition has occurred, this position will inevitably be highly activated and exhibits nucleophilicity that surpasses that of the sydnone, higher adducts will form.

$SbCl_5$ promotes the cycloreversion of donor-acceptor cyclobutane to styrene and methylidene malonate (Scheme 3). Depending on the respective ratio of rate constants, a mixture of the desired product and the methylidene malonate adduct can be isolated. We were able to isolate compound **7 aa** as a side product in the synthesis of product **6 ab**.

We suggest a mechanism that is consistent with our previous work on the Friedel-Crafts type ring-opening of donor-acceptor cyclobutanes[4] and similar works by Moran,[3c] Ghorai,[3d] Kim,[3e,f] Tang,[3g] Kerr,[3h] and Ivanova and Trushkov[3i] (Scheme 4).



Scheme 3. Lewis acid catalyzed cycloreversion of cyclobutane **3 b** to 4-ethoxystyrene and methylidene malonate **4 a**.

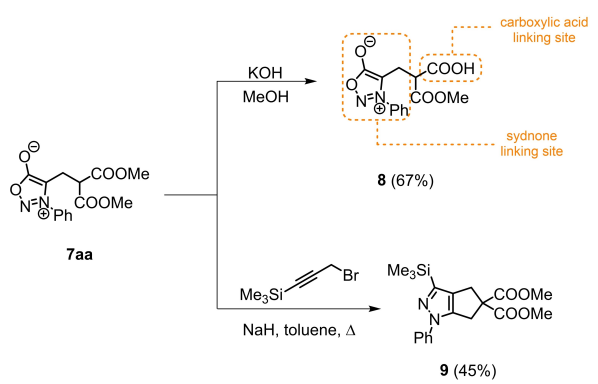


Scheme 4. Probable mechanism of the nucleophilic ring-opening of DACs by sydnones.

The cycle is initiated by coordination of the acceptor-bearing component (here: **DAC**) to $SbCl_5$ forming complex **I**. We cannot say with certainty which attribute of $SbCl_5$ sets it out as the seemingly only viable Lewis acid. $SbCl_5$ is a soft yet very strong Lewis acid and it exists in equilibrium with $SbCl_3$ and Cl_2. We verified experimentally that $SbCl_3$ alone is not catalytically active. However, this does not rule out that a mixture of a Sb(V)-species and Cl_2 is necessary. We did not observe the formation of complex **I-Cl** on LC-MS or GC-MS, however, it remains a viable alternative intermediate that is speculated to play an important role in most metal chloride catalyzed DAC-reactions. Neither have we observed the chlorination of sydnones when stirred with $SbCl_5$ alone. Whether via complex **I** or the alternative pathway of chlorinated intermediate **I-Cl** and the subsequent pseudo-π-complex **I$^{\pi}$-Cl**, pseudo-σ-complex **II** is formed. The regiochemistry of the product rules out the formation of an alkylidene malonate (a formal 1,2-hydride shift) that can often be observed in gallium chloride catalyzed reactions of DACs.[16] Elimination restores the sydnone moiety and protonation of complex **III** releases the final product and reformed catalyst. We propose a similar mechanism for the reaction of cyclobutanes, no ring cleavage is necessary of course for Michael acceptors.

To test our procedure on a larger scale and illustrate the reactivity of our products, we prepared the free mono-acid **8**. The acid moiety is of interest for *in vivo* or *in vitro* linking. Acid **8** is best used quickly as it slowly degrades at room temperature and under the influence of light. Beyond this potential application, our derivatives can be used to construct interesting annulated pyrazoles of varying ring sizes, as illustrated by the one-pot synthesis of compound **9**. Compound **7 aa** can be prepared on large scale (4 mmol) in quantitative yields and without purification by HPLC (see Supporting Information), (Scheme 5).

In conclusion, we have developed a simple protocol for the nucleophilic addition of sydnones to different DACs, DACBs, and strongly activated Michael acceptors; different sydnones can also be employed as well. The procedure enables the late-stage functionalization of sydnones by effectively attaching an



Scheme 5. Potential synthetic use of alkyl malonate bearing sydnone.

alkyl chain of one to three carbon atoms with a terminal malonate group that can be utilized as an additional site for linking (e.g., amidation, esterification). We exemplified the versatility of the products with the one-pot synthesis of an annulated pyrazole.

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Conflict of Interest

The authors declare no conflict of interest.

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